The retinoblastoma (RB) gene family in cellular reprogramming

Grant Award Details

The retinoblastoma (RB) gene family in cellular reprogramming

Grant Type: Basic Biology I

Grant Number: RB1-01385

Project Objective: The overall objective of this projective is to explore the role of the RB gene in reprogramming to iPSC, and potential mechanisms of action of RB during the reprogramming process.

Investigator:

Name:	Julien Sage
Institution:	Stanford University
Type:	PI

Human Stem Cell Use: iPS Cell

Cell Line Generation: iPS Cell

Award Value: $1,357,085

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4 (NCE)

View Report

Grant Application Details

Application Title: The retinoblastoma (RB) gene family in cellular reprogramming

Public Abstract: One important aspect of regenerative medicine is the ability to introduce functional stem cells into patients to restore tissue function. This type of therapeutic approach will not be commonly used until several major potential problems have been addressed, including immune rejection and the risk of developing cancer.

Induced pluripotent stem cells (iPSCs) hold great promise in regenerative medicine: these cells are similar to embryonic stem cells (ESCs) but can be derived upon “reprogramming” of any mature cell type isolated from a patient. Thus, tissue-specific stem cells derived from iPSCs and re-injected into the same patient may not trigger immune rejection. However, before the full potential of iPSCs is achieved, we need to learn how to better generate these cells, control their maturation into tissue-specific stem cells and progenitors, and harness their tumorigenic potential.

Interestingly, ESCs and iPSCs share many characteristics of cancer cells, including their unlimited proliferation potential, and emerging evidence suggests that the mechanisms underlying the infinite proliferation of cancer cells and ESCs are intimately intertwined. Similarly, the progressions stages of tumorigenesis and cellular reprogramming to iPSCs share several characteristics, including changes in the packaging of the chromosomes.

Based on these observations, we propose to directly study the function of a major cancer pathway, the RB pathway, in cellular reprogramming and iPSCs. RB is a key tumor suppressor in humans. RB acts as a cellular brake that restricts cell division but has several other cellular functions, including in the control of cellular maturation. When RB is mutated, cells divide faster and become more immature, two features of cancer cells, but also of cells undergoing reprogramming.

We hypothesize that RB is an important regulator of cellular reprogramming and will test this idea using mouse and human cell types in culture. We believe that these experiments may identify novel and safer ways to induce the generation of iPSCs from adult cells or to improve existing protocols. Understanding the molecular details of the reprogramming process may lead to the development of small molecule compounds that can target precise proteins and/or transcription machinery involved in reprogramming. These experiments may also provide novel insights into the differences and similarities between tumor cells and iPSCs, providing new ways to suppress the tumorigenic potential of iPSCs and ESCs. Finally, better knowledge of the mode of action of RB family members may also allow for a better control of the differentiation of hESCs and iPSCs into tissue-specific stem cell populations.

Statement of Benefit to California:	Human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs) hold the promise of treatments and cures for human diseases that affect millions of people. However, before these cells can be used in the clinic, a better understanding of the mechanisms controlling their proliferation and their capacity to produce a functional progeny is critically required. Our work on how the RB tumor suppressor gene may control the reprogramming of somatic cells into iPSCs may identify novel means to manipulate hESCs, to control the fate of these cells when transplanted into patients. Because hESCs have the capacity to form any type of cell in the human body, these experiments will be relevant to a large number of human diseases. Despite significant decreases in the incidence and mortality rates of cancers in California over the past decade, nearly one out of every two Californians born today will still develop cancer at some point in their lives, and it is likely that one in five persons will die of the disease. Overall, in 2009, more than 50,000 people will die of cancer in California. These statistics underscore the need for the development of novel approaches to detect and treat human cancers. Given the similarities between tumor cells and embryonic cells, our work on the role of the RB tumor suppressor in hESCs and iPSCs may provide novel insights into the mode of action of RB in human cancer cells and may identify novel means to detect and treat cancer patients. Thus, the proposed research may benefit a broad range of patients, from young children to senior citizens, in California and elsewhere.